22. (Original) A cloned transgenic ungulate having the same genotype as the transgenic ungulate of Claim 1, wherein said cloned transgenic ungulate is created using nuclear transfer techniques.

23. (Original) The cloned transgenic ungulate of Claim 22, wherein said ungulate bears a heterologous gene that is extraneous to the prion gene locus.

24. (Original) The transgenic ungulate of Claim 23, wherein said ungulate is a bovine.

25. (Original) The transgenic ungulate of Claim 24, wherein the heterologous gene is operably linked to a mammary-specific promoter, and expression of said heterologous gene enables production of a therapeutic protein in the milk of said transgenic bovine.

26. (Original) A line of transgenic ungulates having the same genotype as the transgenic ungulate of Claim 1.

27. (Original) A line of transgenic ungulates having the same genotype as the cloned transgenic ungulate of Claim 22.

28-49 (Cancelled)

REMARKS

By the present amendments, non-elected claims 10-21 and 31-49 are cancelled. Applicants reserve their right to pursue these claims in a continuation or divisional patent application. Additionally, elected claims 7 and 28-30 have been cancelled. Finally, claims 1, 2, 4 and 8 have been amended. These amendments are introduced in order to obviate all the outstanding §112 issues.

Essentially, claim 1 has been amended such that it is now limited to a transgenic ungulate having a homozygous deletion of the prion gene.

Claim 2 has been amended to delete "or disruption" consistent with the amendment of claim 1.

Claim 4 has been amended to delete reference to "PGK" in relation to the promoter recited therein.

Claim 8 has been amended to change its dependency in view of the cancellation of claim 7.

None of these amendments introduces any new matter into the subject application. These amendments are made to expedite prosecution. It is believed that these amendments obviate all outstanding §112 issues.

Turning now to the Office Action, the election of claims 1-9 and 22-30 without traverse is acknowledged. The restriction requirement is now moot as all the non-elected claims have been cancelled.

Claim 4 stands rejected as being indefinite in the recitation "PGK promoter". This rejection is now moot as "PGK" has been deleted. However, it is respectfully maintained that one skilled in the art would be well aware that "PGK" is a conventional abbreviation for the phosphoglycerate kinase promoter. Applicants note that this promoter is well utilized in recombinant expression vectors and for cloning purposes.

Claim 1 was asserted to lack antecedent basis for "said bovine" in claim 1. This rejection is well taken. Claim 1 has been amended to delete "said bovine". Withdrawal of the §112 second paragraph rejection of claims 1 and 4 is respectfully requested.

Claims 1-9 and 22-30 stand rejected based on §112 first paragraph as allegedly being broader than the enabling disclosure. It is anticipated that this rejection has been obviated by the present amendments.

Essentially, the basis of the rejection seems to be the following:

(i) that homozygous deletion of the ungulate prion gene is enabled but not heterologous deletion or disruption of a prion gene;

(ii) that the specification does not establish that a cloned ungulate containing a disruption or deletion of the prion gene locus will render such ungulate less susceptible to prion-related diseases.

These bases of rejection should now be moot. First, the claims have been amended and require that the cloned ungulate contains a homozygous deletion of the prion gene. Applicants respectfully submit that one skilled in the art could, based on the teachings of this application, effect mutations or insertions in the prion gene locus that disrupt the gene, i.e., inhibit or prevent the expression thereof. This could be effected by disruption of the prion gene reading frame, promoter disruption, or deletion of essential portions of the prion gene. However, in order to expedite prosecution, the claims now require hemozygous deletion of the prion gene which the Examiner acknowledges is enabled by the subject application.

With respect to the second basis of the enablement rejection, i.e., that the specification does not establish a correlation between the claimed mutation and disease resistance, Applicants assume this rejection was made because the claims encompassed previously incomplete prion gene mutations. Certainly, if both copies of the gene are deleted (homozygous deletion) it logically follows that a prion-associated disease will occur at reduced incidence (zero) in the ungulate containing such homozygous deletion. However, as it is not necessary to recite this phenotype property for an understanding of the claims, this phraseology ("unsusceptible to prion-related disease") has been cancelled.

Also, the rejection alleges that the specification does not teach "how to use" cloned ungulates according to the invention. This basis of the rejection is respectfully traversed. Clearly one skilled in the art would well understand that a cloned ungulate lacking both copies of the prion gene would provide a superior animal having many applications.

For example, it would be useful for breeding or agricultural purposes as it would not be prone to diseases associated with said prion gene. Therefore, these animals and progeny thereof would be useful for meat production.

Additionally, such animals would be useful as animal models for study of the effect of prion gene deletion on phenotype. Also, such animals would have potential

applications for the expression of recombinant proteins. Note, e.g., claim 9 that provides for a recombinant bovine [according to claim 1] to comprise a heterologous gene linked to a mammary-specific promoter. With respect thereto, the use of transgenic ungulate for expression of heterologous polypeptides, wherein expression is driven by a mammary-specific promoter is well established. In fact, numerous patents have been granted that are directed to the use of transgenic ungulates to produce heterologous polypeptides in their milk because the expression thereof is driven by a mammary-specific promoter.

Additionally, several patents have been granted that encompass the production of cloned transgenic ungulates (see e.g. US Patent No. 5,945,577 issued to Stice et al. And assigned to the University of Massachusetts). Based thereon the United States Patent Office has acquiesced that transgenic ungulates, e.g., bovines have an accepted usage, e.g., in agriculture and for recombinant protein production.

Thus, based on the foregoing, withdrawal of the §112 first paragraph rejection of claims 1-9 and 22-30 is respectfully requested.

Claims 28-30 stand rejected based on non-enablement grounds. This rejection is moot as all of these claims have been cancelled.

Claims 1-3, 5-9, and 22-27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Weissman et al., 1997 (U.S. Patent No. 5,698,763) in view of Wu et al., 1997 (Methods in Gene Biotechnology, pp339-365) and Shani et al., 1992 (Transgenic Research, Vol. 1(S): 195-208). This rejection is respectfully traversed to the extent it may be applicable to the claims as amended. With respect thereto, the Examiner is respectfully reminded that the claims are now restricted to ungulates having a homozygous deletion of the prion gene

Weissman does not render obvious the claimed methods and animals. While Weissman admittedly teaches providing animals containing prion gene mutations, it shall be noted that the only prion gene sequences actually described therein are of

murine origin. The reference fails to teach or suggest any ungulate prion gene sequence, and more specifically a bovine prion gene sequence or the use thereof.

Also, while the Examiner is correct in indicating that Weissman does prophetically describe making "transgenic animals, such as sheep, pigs and cattle, having deleted prp gene", the specification does not adequately enable or provide written description therefor.

To the contrary, it should be noted that ungulate prion genes, including bovine prion genes, posses DNA sequences very dissimilar to murine prion genes. Also, while there exist some sequence similarities between ungulate and murine prion DNAs, there is no reasonable basis to conclude that one skilled in the art could not use a murine prion gene to produce transgenic ungulates containing homozygous deletions of the prion gene as claimed.

Therefore, Weissman at least taken singularly, does not teach or suggest the claimed invention. However, Weissman has been combined with two secondary references. The first, Wu et al., is cited based on its general disclosure relating to producing transgenic knockout animals. Specifically, this is effected by use of a vector containing appropriate selectable marker genes, and targeting constructs. This reference also does not teach or suggest the amended claims as it fails to teach or suggest DNA constructs that could be used to produce transgenic ungulates containing homozygous deletion of the prion gene. Rather, Wu simply provides support for the premise that methods for making transgenic knockout animals were known prior to the effective filing date of this invention.

The second secondary reference, Shani, is cited based on its disclosure relating to transgenic mice that express a heterologous polypeptide under the regulation of a mammary-specific promoter (sheep BLG promoter). It is concluded that the expression of heterologous polypeptides regulated by mammary-specific promoters was known prior to the invention. However, this reference also fails to teach or suggest the invention as it does not provide or teach any DNA sequence

that could be used to generate a transgenic ungulate bearing a homozygous deletion of its endogenous prion gene.

Therefore, based on the foregoing, withdrawal of the §103(a) rejection of claims 1-6, 8-9, and 22-27 is respectfully requested.

It is anticipated that this response should overcome all outstanding rejections and objections to the specification and claims. Therefore, a Notice Of Allowance is respectfully requested.

However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Also this paper should be considered as a petition for a three-month (3) Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #100375/54379US).

Respectfully submitted,

May 21, 2003

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